June 14, 2021

Professor Hiten RH Patel,
Editor-in-Chief
World Journal of Clinical Oncology

Dear Editor:

We sincerely appreciate the careful review of our manuscript titled **"HER2 targeted therapy in endometrial cancer: clinical and pathological perspectives." (ref. No: 64698)** and the helpful suggestions and comments made by the reviewers. These comments have contributed considerably to the improvement of our manuscript. Do note that all comments from both reviewers have been carefully considered and addressed, and the manuscript has been revised accordingly. The detailed point-by-point responses to the individual comments are provided below.

We greatly appreciate your kind consideration of our revised manuscript and hope that this version is now suitable for publication in *World Journal of Clinical Oncology*. However, we would be pleased to make further revisions if necessary. We look forward to hearing from you at your earliest convenience.

Sincerely yours,

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Responses to the reviewers' comments

Submission to *World Journal of Clinical Oncology*

Manuscript ID: No: 64698 (Invited review)

Title: HER2 targeted therapy in endometrial cancer: clinical and pathological perspectives.

Authors: Ayumi Saito, Hiroshi Yoshida, Tadaaki Nishikawa and Kan Yonemori

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Reviewer #1:

Scientific Quality: Grade C (good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (general priority)

Specific Comments to Authors: This review provides an overview of HER2-overexpression/amplification in endometrial cancer, pathological evaluation methods, and current status of HER2-targeted therapies. HER2 scoring methods in uterine serous carcinoma and carcinosarcoma used in clinical trials were reviewed. Ongoing clinical trials targeting HER2 in endometrial cancer were summarized and discussed. Applying HER2 targeted therapy to type II endometrial cancer is promising but more clinical evidence is required to establish the optimal patient selection (HER2 IHC/ISH scoring). The manuscript provides a timely review of this important subject and I recommend it being accepted after minor language polishing.

General response: Thank you for your encouraging assessment. We have addressed all the comments made by the reviewer and hope that our explanations and revisions are acceptable to you. As indicated in the responses below, the manuscript has been improved according to the reviewer's suggestions.

Specific comments: Please correct the following minor points:

(1) The full forms of abbreviated phrases should be mentioned when they first appear. Abbreviations including MSI-H, MSS, dMMR, pMMR, DISH appear without the full forms mentioned.

Response to comment #1: Thank you for your suggestion; we completely agree with the reviewer. Accordingly, we have described the full forms of abbreviations; microsatellite instability high (MSI-H), microsatellite stable (MSS), mismatch repair deficiency (dMMR), mismatch repair proficiency (pMMR), and dual-color in situ hybridization (DISH).

(2) ERBB2 is the official gene name for HER2. This should be mentioned. For example, "It is encoded by the ERBB2 gene on chromosome 17."

Response to comment #2: Thank you for your suggestion; we agree with the reviewer. Accordingly, we have mentioned this point as follows: "It is encoded by the *ERBB2* gene on chromosome 17." (Page 6, lines 122-123)

(3) A period seems to be omitted in the following sentence (after [42-44]). "HER2 assessment of serous carcinoma has been performed using various methods, mainly based on the breast

cancer criteria [42-44] however, an optimal HER2 testing method specific for endometrial serous carcinoma has not been established in the clinical trial setting. "

Response to comment #3: Thank you for your suggestion; we entirely agree with the reviewer. Accordingly, we have added the period after [42-44]. (Page 9, line 190)

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (general priority)

Specific Comments to Authors: The authors should include the discuss about the anti-HER2 therapy and current immunotherapy statues and resistance mechanisms toward the EC.

General response: Thank you for your encouraging assessment. We have addressed all the comments made by the reviewer and hope that our explanations and revisions are acceptable to you. As indicated in the responses below, the manuscript has been improved according to the reviewer's suggestions.

Specific comments:

1. The authors should include the discuss about the anti-HER2 therapy and current immunotherapy statues and resistance mechanisms toward the EC.

Response to comment #1: Thank you for your suggestion; we completely agree with the reviewer. Accordingly, we have added the description on this point to the revised manuscript as follows: "Several HER2 bispecific antibodies have been developed that simultaneously bind to two distinct HER2 epitopes, the same domain as trastuzumab and pertuzumab[73]. ZW25, one of HER2 bispecific antibodies, is investigated in phase 2 clinical trial of HER2 overexpressed advanced endometrial cancer and carcinosarcomas.

In addition, HER2-directed immunotherapy also has been developed to overcome resistance[19, 74]. The bispecific HER2/CD3 antibodies BTRC4017A, GBR-1302 and M802 induce cytotoxic effect by interaction with HER2 on tumor cell and CD3 on cytotoxic T cell. NJH395 are immune-stimulating antibody conjugates (ISACs) which HER2 antibody links to payload as toll-like receptor7(TLR7) and TLR8. Stimulating TLR activated natural killer cells and antigen-presenting cells and facilitate invasion of CTLs to tumor tissues. PRS-343 increases tumor lymphocyte invasion via targeting HER2 and CD137(4-1BB). CD137 is known as a co-stimulating

factor of T cell activation. HER2-directed immunotherapy is expected future development in HER2-positive tumors." (Pages 16-17, lines 352-372)

Science editor:

1 Scientific quality: The manuscript describes a review of the HER2 targeted therapy in endometrial cancer. The topic is within the scope of the WJCO. (1) Classification: Grade B and Grade C; (2) Summary of the Peer-Review Report: The review provides an overview of HER2-overexpression/amplification in endometrial cancer, pathological evaluation methods, and current status of HER2-targeted therapies. However, the authors should include the discussion about the anti-HER2 therapy and current immunotherapy statues and resistance mechanisms toward the EC; and (3) Format: There are 2 tables and 2 figures. (4) References: A total of 74 references are cited, including 26 references published in the last 3 years; (5) Self-cited references: There are 2 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade B and Grade B. A language editing certificate issued by Editage was provided. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJCO. 5 Issues raised: (1) The title is too long, and it should be no more than 18 words; (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (3) The column should be minireviews. 6 Recommendation: Conditional acceptance.

General response: Thank you for your positive assessment.

(1) The title is too long, and it should be no more than 18 words;

Response to comment #1: Thank you for your comment. The present form of the title is "HER2 targeted therapy in endometrial cancer: clinical and pathological perspectives." If this title is still too long, we are going to change this title.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows

or text portions can be reprocessed by the editor;

Response to comment #2: Thank you for your comment. Accordingly, we have provided the original figures as a ppt file.

(3) The column should be minireviews.

Response to comment #3: Thank you for your comment. We agree with you that this manuscript would be presented as a minireviews.

Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

General response: Thank you for your positive assessment. We have addressed all the comments made by the reviewers and updated the manuscript in accordance. We hope that you find our explanations and revisions acceptable.

Thank you again for your valuable comments. We are grateful for the time and energy spent making these observations and recommendations.